

/application-reviews/AP1-08048

**AP1-08048: Development of a Phase II Study of Stem Cell Gene Therapy for Sickle Cell Disease**

**SCORES AND RECOMMENDATIONS**

**Score:** <65

**GWG Recommendation:** Not recommended for funding

**Public Abstract (provided by applicant)**

Sickle cell disease (SCD) results from an inherited mutation in the hemoglobin gene that causes red blood cells to "sickle" under conditions of low oxygen and block small blood vessels in vital organs. It occurs with a frequency of 1/500 African-Americans, and is also common in Hispanic-Americans, who comprise up to 5% of SCD patients in California. The median survival based on 1991 national data was 42 years for males and 48 years for females. More recent data indicate that the median survival for Southern California patients with SCD is only 36 years, suggesting that serious problems exist regarding access to optimal medical care in this community. By 20 years of age, 15% of children with SCD suffer major strokes and by 40 years of age, almost half have had central nervous system damage leading to significant cognitive dysfunction. These patients suffer recurrent damage to lungs and kidneys as well as severe chronic pain that impacts on quality of life.

While current medical therapies for SCD can make an important difference in short-term effects, the progressive deterioration in organ function results in compromised quality of life and early deaths in populations who are generally adversely affected by health care disparity. Transplantation of bone marrow from a healthy donor as a source of new adult blood-forming ("hematopoietic") stem cells can benefit patients with SCD, by providing a source for life-long production of normal red blood cells. However, hematopoietic stem cell transplantation is limited by the availability of well-matched donors and by the immune reactions that may occur between the cells of the donor and the patient. Thus, despite major improvements in clinical care of SCD patients, SCD continues to be a major cause of illness and early death.

The stem cell therapy approach to be developed by this group will be used to treat patients with SCD by transplanting them with their own bone marrow adult hematopoietic stem cells that are genetically corrected by adding a designed hemoglobin gene that blocks sickling of the red blood cells. This approach has the potential to permanently cure this debilitating illness with significantly less toxicity than with a bone marrow transplant from another person. A Phase I clinical trial using stem cell gene therapy for patients with SCD is being performed by this multi-disciplinary Disease Team, combining world-leading experts in stem cell gene therapy, clinical bone marrow transplantation and the care of patients with SCD. The goal of this Accelerated Development Pathway proposal is to extend the studies to more patients to further assess the potential benefits. New approaches to produce the gene delivery vector and for stem cell processing will be developed and used to support a Phase II clinical trial. Successful use of stem cell gene therapy for SCD has the potential to provide a more effective and safe treatment for a larger proportion of affected patients.

**Statement of Benefit to California (provided by applicant)**

Development of methods for regenerative medicine using genetically-corrected human stem cells will result in novel, effective therapies that improve the health for millions of Californians and tens of millions of people world-wide. Sickle cell disease (SCD) is an inherited disease of the red blood cells that results from a specific hemoglobin gene mutation. SCD disproportionately afflicts poor minority patients in the State of California, causing severe morbidity, early mortality and high medical costs. We will develop and perform a Phase II clinical trial to evaluate the efficacy of a novel treatment for patients with SCD, using their own adult blood-forming stem cells, after correcting the hemoglobin gene defect. Successful treatment of SCD using adult blood forming "hematopoietic" stem cells corrected with gene therapy may provide a clinically beneficial way to treat SCD with greater safety and wider availability than current options. The clinical trial to be performed will treat SCD patients from across the state of California at Southern and Northern California clinical sites. All scientific findings and biomedical materials produced from the studies will be publicly available to non-profit and academic organizations in California, and any intellectual property developed by this Project will be developed under the guidelines of CIRM to benefit the State of California.

**REVIEW SUMMARY**

The therapeutic candidate for the Parent Award, and the subject of this application, is an autologous stem cell gene therapy for the treatment of sickle cell disease (SCD). The IND for the Phase 1 clinical trial funded under the Parent Award is approved by the FDA and is on schedule to open enrollment of adult patients with SCD. The production process for the candidate therapy to be used for the Phase 1 clinical trial results in a level of gene transfer to stem cells which is likely to be therapeutic and may decrease disease severity. However, more effective production of genetically modified hematopoietic stem cells (HSC) will be required for the larger, later clinical trials. For this application, three modules of activity were proposed. Module 1 describes activities to improve vector production quality for higher titer and gene transfer activity. In Module 2, the applicant proposes to improve cell processing by enriching HSC to greater purity prior to gene transfer, which could decrease the amount of vector needed. In Module 3, the applicant proposes to combine the results of activities proposed in Modules 1 and 2 to translate the most effective methods for production of genetically modified HSC into a Phase 2 clinical trial for SCD.

#### **Clinical Competitiveness and Impact of the Proposed Therapy**

- There is a large unmet medical need for a less toxic, lower risk therapy for SCD.
- If successful, the impact of the stem cell gene therapy could be considerable, as the approach is potentially curative and would allow treatment of patients not eligible for allogeneic HSC transplant.
- Several other competing technologies for SCD are also in early development, some of which may have clear logistical and technical benefits over the proposed approach to treating SCD.

#### **Strength of the Development Program**

- The reviewers commended the team for successful filing and clearance of the IND for a first in human stem cell gene therapy Phase 1 clinical trial for SCD. The team has a clear path for evaluating the therapeutic candidate. However, the reviewers thought that the activities proposed in this application would not accelerate the team's overall development program.
- Process development changes are proposed in Module 2 that would select an enriched HSC population for gene modification and subsequent administration in the Phase 2 clinical trial proposed in Module 3. Thus, it is unclear whether the approved Phase 1 clinical trial, which will use the originally characterized stem cell gene therapy, would significantly inform or accelerate a successful Phase 2 trial utilizing a different gene-modified cell product.
- The reviewers raised concerns about the current manufacturing process for the product, which could limit commercial viability of this program.

#### **Qualifications of Development Team**

- The team, along with their clinical investigators, is exceptionally qualified and has a strong track record in stem cell gene therapy.

#### **Progress on Parent Award and Effective Program Leadership**

- Reviewers agreed that the team has made admirable progress on the activities funded under the Parent Award and have achieved IND approval.

#### **Relevance of the Therapeutic to Regenerative Medicine**

- The relevance of the candidate to regenerative medicine is considered to be very high. The proposed gene modified stem cell has proven antecedents and a clear therapeutic rationale for this disease indication. A successful therapeutic could have impact for a variety of related diseases.

#### **Proposed Activities for Acceleration of the Development Program**

- Reviewers saw that incorporation of the proposed activities in Modules 1 and 2 could pose major regulatory challenges for the development program. As the proposed changes in the manufacturing process would result in a different final product than that for which an IND has been approved in the Parent Award, equivalency and safety of the new product would need to be confirmed in preclinical studies, which could have major impact on timelines and progress to clinic.
- Reviewers agreed with the need for improved vector production to achieve higher titer and gene transfer activity. However, there was concern that the approach proposed in Module 1, may not address the underlying limitations of the globin gene vectors. The applicant did not provide sufficient evidence that the proposed scale up process would result in a higher titer vector with increased transduction efficiency and low toxicity.
- Reviewers agreed that improvement in the transduction efficiency of HSC would add value, and were intrigued by the preliminary data presented in support of the work proposed in Module 2. However, reviewers did not see sufficient evidence of a possible

mechanism of action for the increased transduction efficiency, which lowered their enthusiasm for the proposal.

- In Module 3, the applicant proposed to expand administration of the candidate therapeutic in a Phase 2 clinical trial to a wider age range of patients. Reviewers commented that this would require further justification and Regulatory review, and they were concerned that the FDA may not agree with the expansion, given that a different level of risk assessment could be appropriate for the additional patient population.

#### **Feasibility of Proposed Activities for Acceleration of the Development Program**

- Reviewers did not think that the activities proposed in Modules 1-3 would accelerate progress toward more rapid demonstration of clinical proof of concept for the stem cell gene therapy in SCD.

- Reviewers expressed that the activities proposed in Module 1 were not presented with sufficient clarity and quantifiable success criteria to allow assessment of their feasibility. The lack of a detailed, milestone-based development plan with the external vector production organization was considered a weakness of the proposal.

- Reviewers felt that the applicant has given insufficient consideration to the significant loss and potential damage of HSC that would occur during the extra isolation steps proposed in Module 2. Moreover, some of the reagents and equipment that would be used for the isolation and purification of the HSC are currently unavailable and the success of the project is dependent on the availability of these components. Any delay in their availability would impact the proposed timelines, which reviewers described as already unrealistically aggressive.

- The Phase 2 clinical trial proposed in Module 3 would incorporate the process modifications identified in Modules 1 and 2 and could not begin until after their completion. Under the proposed timeline, the Phase 2 trial is not scheduled to initiate until late 2017 and the planned clinical efficacy data would be collected at 6 months after treatment. Thus, it would not be possible to evaluate the impact of the proposed improvements to accelerate demonstration of clinical proof of concept by 2017, which is a stated goal of this RFA.

#### **Conflicts:**

Carol Danielson

---

**Source URL:** <https://www.cirm.ca.gov/our-funding/application-reviewsap1-08048>